Programs of alternative splicing regulation by polypyrimidine tract binding protein

Grant Award Details

Programs of alternative splicing regulation by polypyrimidine tract binding protein

Grant Type: Basic Biology II

Grant Number: RB2-01502

Project Objective: The goal is to identify changes in splicing that occur as hESC differentiate into neural progenitor cells and then into neurons. Focus on sub-network of changes regulated by PTB and nPTB proteins.

Investigator:

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Type:	PI

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $1,344,562

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: NCE

View Report

Grant Application Details

Application Title: Programs of alternative splicing regulation by polypyrimidine tract binding protein

Public Abstract: The therapeutic promise of stem cell biology lies in its potential for cell replacement therapies in diseases where an essential cell type of the patient malfunctions or degenerates. This is particularly evident in diseases of the nervous system where cells largely lose their ability to proliferate and thus regenerate after embryonic differentiation. Devastating neurodegenerative disorders, such as amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA), are characterized by a progressive paralysis caused by motor neuron death and currently have no cure. Strategies for replacing specific neuronal cell types with cells derived from human embryonic stem (hES) cells will require understanding the genetic programs that control hES cell differentiation. These rapidly dividing pluripotent cells undergo a major transition in gene expression to become neuronal progenitor cells (NPC), while maintaining their proliferative ability. Another drastic change in gene expression program occurs as NP cells differentiate into neurons, where cell division has stopped. A great deal of important work is describing the DNA level changes that control gene expression in ES cells and during their transition to NPC and neurons. However, the production of a protein product from a gene is controlled at each step in the gene expression pathway where the DNA gene is first transcribed into RNA and the RNA then translated into protein. An important RNA level regulatory step in this pathway is the processing of the primary RNA transcript from the gene into an mRNA that can be translated into protein. One part of this processing is the pre-mRNA splicing reaction, where alternative splicing patterns in the pre-mRNA determine the structure of the final protein product of most human genes. Little is known about how this step in the gene expression pathway is regulated in ES cells or during their differentiation. Yet ALS and SMA can both be caused by the loss of components of the splicing machinery and a great deal of work is examining how splicing might be disrupted in mature neurons of ALS and SMA patients. In this study, we will examine how two important splicing regulators, the polypyrimidine tract binding protein (PTB) and its neuronal homolog nPTB, affect splicing in normal ES and NP cells. We will characterize the programs of regulation controlled by these proteins. In particular, we will focus on those parts of the PTB regulated splicing program that affect cell proliferation and the ability of ES and NP cells to self renew. From this work, we will advance our understanding of how ES cells differentiate into neurons and how pre-mRNA splicing controls cell function in normal development and in disease.

Statement of Benefit to California: Neurological diseases affect millions of patients in California and elsewhere. For example, spinal muscular atrophy (SMA) is one of the most common genetic causes of infant death and has no effective treatment. SMA and other neurological diseases are caused by errors in the cellular process of pre-mRNA splicing. One promising strategy for neurological treatments is in cell replacement therapies using hES and iPS cells as source material for regenerating normal neurons in place of those lost to the disease. Another therapeutic strategy for SMA is in drugs that alter the splicing process to improve its efficiency in diseased cells. This project will examine the splicing process in normal hES cells and how it is regulated when these cells differentiate into neuronal progenitor cells and neurons. This will provide essential information on the biology of stem cells needed to move towards various therapeutic applications. The project will also provide a system for drug discovery in the new field of splicing targeted therapeutics. This work will help California to continue to lead in these areas of basic research, as well as provide the state with a head start in biotechnology and pharmaceutical development for the practical application of these discoveries.